White-Paper

What Studies Are Appropriate to Use to Estimate Health Impacts from Specific Sources Such as Diesel PM?

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1 There Are Many Unresolved Issues with the PM 2.5 Epidemiology

1.1 Reported associations for $PM_{2.5}$ are not equivalent to causation

The California Air Resources Board (CARB) has expressed interest in understanding the potential health impacts of near-roadway exposures to vehicle emissions, focusing primarily on diesel exhaust particles (DEP). Epidemiologic studies have reported statistical associations between ambient PM (due in part to vehicle traffic intensity) and mortality and morbidity (increased respiratory symptoms and decreased pulmonary function). These effects cannot be directly linked to DE and DEP, because there are other contributing sources to near-roadway exposures such as road dust, brake wear, tire wear, and gasoline engine exhaust. Even more important, there are major uncertainties and assumptions inherent to the interpretation of PM-mortality associations reported in epidemiology studies. For example, the cohort (ACS) studies have shown that mortality rates vary widely from city to city for reasons not understood. The time series (NMMAPS) studies have shown that the PM "effect factors" very from city to city, with some cities showing reduced mortality with increasing PM. The "explanatory effect" of PM in both cases is small.

1.2 Problems with assuming causality from single-pollutant associations

The epidemiologic associations between ambient PM-2.5 levels and morbidity and mortality rates have been based on "opportunistic" data, in that these correlative analyses relied on air monitoring designed for other purposes (*i.e.*, NAAQS compliance). And, the mortality and morbidity statistics used in the PM-epidemiology studies were collected for routine tracking of US public health by the National Center for Health Statistics. Because the correlations reported are between population statistics and central-monitor PM-2.5 levels (*i.e.*, exposure at the population level), these studies are ecologic or semi-ecologic in nature. (or semi-ecologic in the case of the cohort studies). Gary Taubes, in his article "Epidemiology Faces Its Limits," (1995), summarized the numerous uncertainties associated with observational epidemiological studies, and the difficulty in assigning a meaning or causal basis to reported associations. In their article "Time Series Analyses of Air Pollution and Health: Straining at Gnats and Swallowing Camels," Lumley and Sheppard (2003) also emphasized the daunting challenges faced by air pollution epidemiologists:

> "Estimation of very weak associations in the presence of measurement error and strong confounding is inherently challenging. In this situation, prudent epidemiologists should recognize that residual bias can dominate their results. Because the possible mechanisms of action and their latencies are uncertain, the biologically correct models are unknown. This model selection problem is exacerbated by the common practice of screening multiple analyses and then selectively reporting only a few important results."

As discussed extensively by Taubes, smaller RRs (*i.e.*, RR<3) are generally considered to be weak in nature and to require other lines of evidence (*e.g.*, toxicological evidence, highly plausible biological mechanism) to demonstrate causality. As discussed recently by Boffetta *et al*. (2008) and Fewell *et al*. (2007), it is plausible that RRs on the order of 1.5 to 2.0 can be explained by residual and/or unmeasured confounding. Given well-known examples of epidemiological false-positives that include erroneously predicting increased risk of pancreatic cancer from coffee drinking and erroneously predicting a protective effect from hormone replacement therapy (HRT) on heart attack risk in postmenopausal women, prudent public health policy requires caution when relying exclusively on RRs < 2, let alone RRs that barely exceed 1.0, without confirmatory evidence from other kinds of health-effects studies, including human clinical studies and animal toxicology, both of which are available for DEP.

Among the uncertainties inherent to the interpretation of associations reported in air pollution epidemiology studies are the following. Epidemiological studies often include zero effect in the range of effects reported, and the model analyses incorporate many assumptions that can markedly affect the results obtained. Problem areas include: (1) model specification, (2) treatment of co-pollutants [both measured and unmeasured], (3) correction for seasonal trends, (4) exposure misclassification / measurement error, (5) actual years of life lost for the calculated "deaths," (6) effect modifiers [*e.g.*, educational achievement], (7) corrections for seasonal and day-to-day variations in risk factors, and (8) the fact that variation in results by locale bears little or no relation to PM-2.5 composition at that locale.

These problems for PM-2.5 and other criteria air pollutants have received extensive commentary (*e.g.*, Gamble, 1998; Gamble and Nicolich, 2000; Keatinge and Donaldson, 2001; Green *et al*., 2002; Phalen, 2002; Stieb *et al.*, 2002; Valberg, 2004; Koop and Tole, 2004; Moolgavkar, 2005, 2006; Henderson, 2006; Keatinge *et al*. 2006). It is now clearly recognized that the role of specific constituents of air pollution in the associations remains highly uncertain and not understood. Daily mortality can be statistically correlated not only with PM, but also with all other common air pollutants (*e.g.*, the criteria pollutants carbon monoxide, ozone, nitrogen dioxide, and sulfur dioxide), as well as with non-criteria pollutants (Hagen *et al*., 2000; Oftedal *et al*. 2003). That is, for ambient PM, for a variety of ambient criteria pollutant gases, and for other airborne chemicals, daily fluctuations in concentrations are found to correlate with health statistics. Stieb and colleagues (2002) performed meta-analyses using 109 time-series studies that reported associations

between daily mortality rates and criteria-pollutant concentrations in ambient air. The following list provides Stieb *et al*.'s reported estimates of percent increases in all-cause mortality (and 95% confidence intervals) associated with an increment in ambient air levels for each criteria pollutant of a size equal to the representative mean ambient concentration for that pollutant. Notably, they found each association to be statistically significant (SS). For the criteria pollutants, Stieb *et al*. (2002) found that the following percentage increments in daily mortality correlated with increases in each substance:

Carbon monoxide:	+1.7% (1.2 – 2.2%)
Nitrogen dioxide:	+2.8% (2.1 – 3.5%)
PM_{10}	+2.0% (1.5 – 2.4%)
$PM_{2.5}$	+2.0% (1.2 – 2.7%)
Ozone	+1.6% (1.1 – 2.0%)
Sulfur Dioxide	+0.9% (0.7 – 1.2%)

Such positive, statistically significant results might be interpreted to suggest that, for each one of the criteria pollutants, present-day atmospheric levels are acutely deadly. But, studies in laboratory animals and elevated PM exposures in humans demonstrate that the concentrations at which these substances can cause death are thousands of times higher than ambient levels. This represents a dramatic contradiction between the correlative, epidemiologic studies on PM-2.5 *versus* laboratory-animal and human clinical data on DEP exposure.

Not only is it unclear which (if any) criteria pollutant(s) underlie the epidemiologic associations, but also other airborne pollutants, called "hazardous air pollutants" or HAPs (*e.g.*, formaldehyde, methanol, benzene, 1,3 butadiene), can be expected to co-vary with PM-2.5 levels. However, HAPs levels are not routinely measured, and hence, it has not been possible to rule out a role of HAPs in reported PM associations.

1.3 The PM-health-effect associations show troublesome inconsistencies

Even aside from the uncertainty as to the causal basis of "associations" between ambient PM-2.5 levels and health statistics, there are a number of prominent epidemiological studies that have found either no correlation between health impacts and increased $PM_{2.5}$, or "protective" effects of air pollutants, including in locales with elevated PM-2.5 concentrations [*e.g.*, the Venners *et al*., 2003, study of daily mortality in the district of Chongqing, China, where a mean PM-2.5 concentration of 147 $\mu g/m^3$ was reported, yet negative (not statistically insignificant) associations were found between daily mortality and mean daily $PM_{2.5}$ were observed on all days]. As discussed subsequently in **Section 1.3**, other studies have identified very important

factors (*e.g.*, stress and activity patterns) that are likely confounders of air-pollution *vs*. health-effect associations.

The 90-city National Morbidity, Mortality, and Air Pollution Study (NMMAPS) investigated the relationship between daily ambient PM-10 levels and daily mortality in 90 of the largest US cities, using data collected from 1987 to 1994. The original study report was issued in 2000, but it turned out there were problems with the model fitting software. Compared to the 2000 publication, the re-analysis showed reduced PM effect factors and revealed considerable heterogeneity among the "PM effect factors" [1] for individual cities, with more than one-third of the cities showing negative associations between mortality and ambient PM_{10} levels (meaning that PM_{10} increases were associated with decreases in mortality) and only two cities showing positive and statistically significant PM effect factors (New York at 0.8%, with a PM_{10} mean level of 28.8 $\mu g/m^3$; and Oakland at 1.6%, with a PM_{10} mean level of 26.3 $\mu g/m^3$) based on the updated maximum likelihood estimates (new) obtained for the general linearized model (GLM) with natural splines for covariates. Examination of the updated NMMAPS city-by-city results reveals that several of the cities in the Southeast U.S. (*i.e.*, Jackson, MS; Nashville, TN; Knoxville, TN; Atlanta, GA) show negative associations between total mortality and PM_{10}, as well as between cardiovascular and respiratory mortality and PM_{10}, meaning that higher ambient PM_{10} levels correlate with decreases in mortality (Dominici *et al*., 2003).

Furthermore, the NMMAPS city-by-city results also suggest that the actual level of PM does not affect the PM associations with health outcomes, which is strangely contradictory to toxicology. Figure 1 below illustrates the heterogeneity in the NMMAPS results, showing that neither the direction (positive or negative) nor the magnitude of the PM effect factor is related to the average PM_{10} concentrations in the study cities. The heterogeneity is highlighted by the fact that the PM effect factor for the US city with the lowest PM levels (Honolulu) is in fact slightly greater than the PM effect factor for the US city with the highest PM levels (Riverside), although neither result is statistically significant. Although differences in PM composition may be one possible explanatory factor for the city-by-city heterogeneity, differences in potentially confounding factors are another possible explanation.

Another major study is the American Cancer Society (ACS) prospective cohort study, which focused on PM-2.5 and covered about 151 metropolitan areas, with the initial analysis covering 1982 to 1989. The ACS cohort yielded a number of results that suggest the PM-mortality associations may not be causal. First of all, the comprehensive Krewski *et al*. (2000) reanalysis of the ACS cohort concluded that effects of co-pollutants were important, and adjustment for co-pollutants decreased the PM risk estimate. For example,

[1] PM "effect factors" are typically given in units of "percent change in mortality" per "10 $\mu g/m^3$ change in PM concentration."

Table 47 in the Krewski *et al*. reanalysis showed that when the PM relative risk for all-cause mortality was adjusted for gaseous co-pollutants (and SO_2 in particular), the relative risk (RR) was reduced to nearly unity (1.0), *i.e*., there was no increased risk from fine PM. Thus, the use of concentration-response functions based on single-pollutant models can result in overestimation of the health impacts attributable to PM, because such statistical associations may include the effects of other ambient pollutants (both measured and unmeasured), as well as other uncontrolled variables (*e.g*., meteorological variables, geographical location variables, and other risk factors). The Krewski *et al*. authors concluded:

> We observed a stronger association between sulfur dioxide levels and mortality from all causes in the ACS Study than between either fine particles or sulfate and all cause mortality." (p. 224)

Secondly, the Pope *et al*. (2002) reanalysis discovered a number of inconsistent and unexplained results in the ACS study cohort data, *e.g.*, correlations that showed:

(a) immunity from PM-associated mortality with increasing educational level;
(b) reduced PM-associated cardiopulmonary and cancer mortality with increased smoking history;
(c) a protective effect of ambient carbon monoxide against cardiopulmonary mortality and lung cancer mortality;
(d) a protective effect of ambient total suspended particles ("TSP") against lung cancer risk;
(e) a protective effect of PM against all-other cause mortality (non-cardiopulmonary, non-cancer) that depended on which of the alternative modeling approaches was used; and
(f) a protective effect of ambient ozone on lung cancer mortality.

In the ACS study, individual-level factors cannot be accounted for because the individuals in the ACS study filled out only one questionnaire, back in 1982. In fact, it is unclear how the study authors dealt with city-to-city relocation of enrolled individuals in the time period between 1982 and the present. As stated in Pope *et al*. (2002),

> "The data on smoking and other individual risk factors, however, were obtained directly by questionnaire at time of enrollment [1982] and do not reflect changes that may have occurred following enrollment. The lack of risk factor follow-up data results in some misclassification of exposure, reduces the precision of control for risk factors, and constrains our ability to differentiate time dependency."

Furthermore, a subsequent Pope *et al*. (2004) reanalysis reported findings indicating a protective effect of long-term $PM_{2.5}$ exposures on diseases of the respiratory system. Specifically, Pope *et al*. (2004) reported that a 10 $\mu g/m^3$ increase in average $PM_{2.5}$ levels was associated with an 8% decrease in diseases of the respiratory system, with this finding achieving statistical significance (RR=0.92, 95% CI: 0.86-0.98).

Similar to the ACS study, the Harvard Six-City study is another long-term cohort study of the health effects of air pollution, consisting of a cohort of approximately 8,100 adults in six U.S. communities

(Watertown, MA; Kingston and Harriman, TN; St. Louis, MO; Steubenville, OH; Portage, Wyocena, and Pardeeville, WI; and Topeka, KS). While the original Dockery *et al*. (1993) analysis of data from a 14-to-16-year mortality follow-up (1974 to 1989) reported a statistical association between $PM_{2.5}$ and excess mortality, it is also important to note that Dockery *et al*. (1993) reported similar associations for nearly all of the other pollutants considered in their analyses, namely sulfate, sulfur dioxide, and nitrogen dioxide. As noted by Krewski *et al*. (2000), who re-analyzed the Dockery *et al*. (1993) data, the Harvard Six-City study findings may be more reflective of the adverse health effects of the overall air pollution mixture rather than of any one constituent, such as PM:

> "The Six Cities Study, with its small number of cities and high degree of correlation among the air pollutants monitored, did not permit a clear distinction among the effects of gaseous and fine particle pollutants. Indeed, estimates of the relative risk of mortality from all causes were similar for exposure to fine particles, sulfate, sulfur dioxide, and nitrogen dioxide. Of the gaseous co-pollutants in the Six Cities Study, only ozone did not display an association with mortality."

These findings for both short-term (NMMAPS) and long-term (ACS and Harvard Six-City) studies illustrate that one cannot establish that a causal basis exists between all PM types and various mortality and morbidity health endpoints based on statistical "associations" reported for PM and health. In addition to the results discussed above, a number of publications report a failure to detect a statistically significant correlation of PM levels with health impacts, or identify flaws in the associations. Although there are a greater number of publications reporting a positive PM association *vs.* those reporting a null result, the reason for the heterogeneity in results is unknown. It should be remembered that "publication bias" may prevent many negative studies from reaching the peer-reviewed literature. Also, for those studies reporting a positive association, the models used to yield this result are variable, that is, authors will often try different analyses, and upon finding one that gives a positive association, publish the result. Finally, each published article tends to be remembered for the positive results it reported, although each study may have tested numerous other associations, finding several that were null in their study but not null in other studies.

Furthermore, PM epidemiological studies have also observed peculiarities in dose-response that are inconsistent with toxicological principles, such as seemingly increased potency of PM at low concentrations compared to high concentrations. As an example, in his time-series analysis of associations between air pollution and daily mortality in Cook County, Illinois, Moolgavkar (2003) reported significant departures from linearity for PM effects. Specifically, Moolgavkar (2003) observed an actual decrease in risk with increasing PM_{10} concentrations above about 50 $\mu g/m^3$. Abrahamowicz *et al*. (2003) observed a similar phenomenon in their re-analysis of the ACS prospective cohort data, with stronger effects of fine particles in the lower range of 10 to 16 $\mu g/m^3$ than at higher concentrations. This attenuation of PM effect factors, and

even reversal of risk at higher PM concentrations, is discordant with biologically plausible hypotheses regarding mechanisms of harm. Findings such as these of non-linearities in dose-response relationships raise additional uncertainty regarding the biological plausibility of epidemiological associations and their reliability for inferring health impacts.

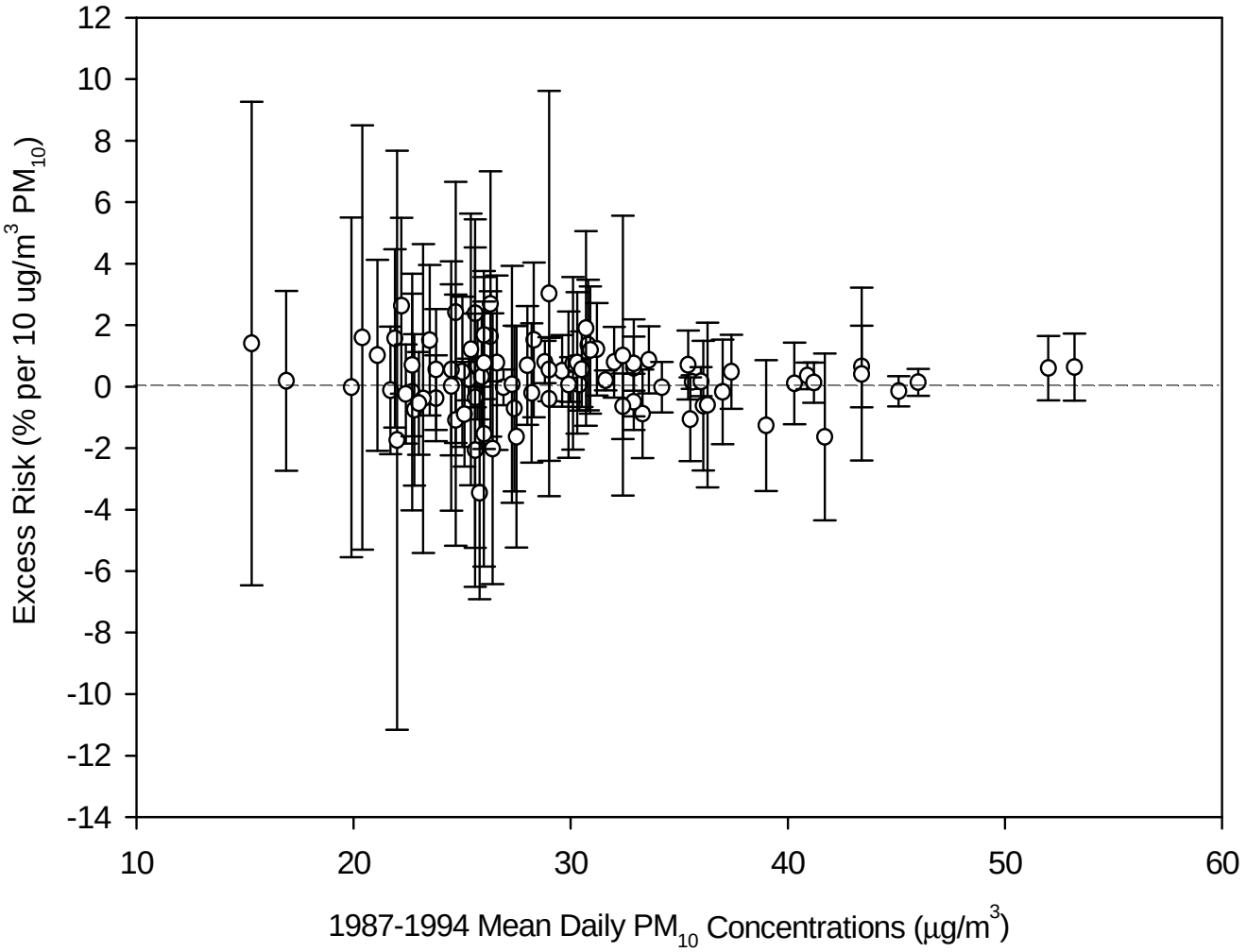


Figure 1.
City-specific PM_{10} mortality increments *vs.* mean daily PM_{10} concentrations for the NMMAPS cities. The two cities with the highest PM_{10} concentrations are Riverside, CA and Bakersfield, CA. Honolulu, HI, is the lowest. Mean daily PM_{10} concentrations and revised PM_{10} excess risks were obtained from http://www.ihapss.jhsph.edu/data/NMMAPS/.

1.4 Non-pollutant factors may play a role, and have not been ruled out

There are a variety of potential confounding variables, many of which are either inadequately controlled or uncontrolled in air pollution epidemiological studies, that may contribute to or even entirely explain epidemiological associations reported for PM-2.5 and adverse health effects. The diseases considered in air pollution epidemiological studies have multiple known risk factors. Yet, psychosocial factors that are shown in the medical literature to be related to such adverse health outcomes as heart attack risk and premature mortality are rarely if ever considered in air pollution epidemiological studies. Although epidemiological analyses typically attempt to address known confounding variables such as time trends, temperature, season, and weather, recent studies have demonstrated how difficult it is to remove these potential effects from the associations.

An HEI expert panel emphasized the sensitivity of the epidemiologic findings to the analytic methods used, and in particular, for different specifications for confounding variables, such as time and weather (HEI, 2003). The HEI Special Panel, which had been convened to address a widespread problem in air pollution epidemiology studies involving the improper application of a popular statistical analysis software program, also determined that substantial uncertainties remain regarding model specification in epidemiological investigations and proper control of potential confounders:

> "Neither the appropriate degree of control for time in these time-series analyses nor the appropriate specification of the effects of weather, has been determined. This awareness introduces an element of uncertainty into the time-series studies that has not been widely appreciated previously. At this time, in the absence of adequate biological understanding of the time course of PM and weather effects and their interactions, the Panel recommends exploration of the sensitivity of these studies to a wider range of alternative degrees of smoothing and to alternative specifications of weather variables in time-series models."

In addition, the HEI Special Panel concluded that the remaining uncertainties in epidemiological studies have served to decrease the level of confidence that can be placed in these studies, while increasing the weight that must be placed on other types of studies, *i.e.*, studies in human volunteers and laboratory animals:

> "Further, uncertainty regarding the estimates of effect from time-series studies can also be expected to place additional emphasis on long-term air pollution studies, on studies of natural experiments (the so-called quasi-experimental studies), and on human experimental and animal toxicologic studies."

In addition to the HEI expert panel, a renewed appreciation of the potential confounding role of weather and temperature in the PM associations has been recognized by others. Keatinge, 2002; Keatinge and Donaldson, 2001; 2006 have pointed out that, in order to adequately correct for the important effects of

temperature and other weather factors, they need to be entered as confounding variables at multiple simultaneous time lags, not just one time position, as has been the practice up to now. When this was done for London data covering 1976-1995, it was found that the "data confirmed that the large, delayed increase in mortality after low temperature is specifically associated with cold, and is not due to associated patterns of wind, rain, humidity, sunshine, SO_2 CO, or smoke" (Keatinge and Donaldson, 2001). A subsequent study that focused on the effects of hot weather found that: "With allowance for [heat stress] confounding factors, generalized additive modeling showed no significant mortality due to ozone, PM, or sulfur dioxide" (Keatinge and Donaldson, 2006).

The PM associations cannot differentiate effects arising from different criteria pollutants, HAPs, or different PM constituents. More importantly, non-pollutant factors correlated with PM-2.5 may cause day-to-day variations in mortality. For example, a recent analysis of correlations between heart attack risk and subjects' daily activities (Peters *et al*., 2004) reported a role for "exposure-to-traffic" stress in heart attack risk. This link between "use of vehicle" and "onset of myocardial infarction" related increased heart attack risk with "presence of traffic," even apart from any pollutant exposure. In fact, the Peters *et al.* investigators found no association of heart attack risk with air pollution variables (Tosteson and Greenbaum, 2005). [2] That is, any increase in heart attack risk likely arose from stress factors such as noise, anxiety, and anger that often accompany driving and commuting.

Furthermore, in a recent, large case-crossover study of the relationship between acute myocardial infarction (AMI or heart attack) and physical exertion, Von Klot *et al*. (2008) analyzed data for over one thousand patients who reported physical activity on the day of the AMI and three days preceding the event. Compared to light or no exertion, the risk of heart attack after strenuous activity was increased nearly 6-fold (RR = 5.7; 95% CI 3.6-9.0). In addition, the authors found that even moderate exercise was significantly associated with increased risk of an AMI (RR = 1.6; 95% CI: 1.2-2.1). Interestingly, no air pollution variables were considered in this study, which instead showed increases in relative risks with increased exertion level, demonstrating a dose-response between the stress of activity and risk of AMI.

Confounding by day-to-day stress levels is supported by the known role of stress as a strong risk factor in cardiovascular deaths (RR up to ~ 25) (Moller *et al*., 1999; 2005; Koton *et al*., 2004; Culic *et al*., 2005). Thus, the weak RR's in mortality-PM time-series associations could easily arise from uncontrolled confounding by population stress factors. Noise stress is one component of traffic that is known to increase risk of adverse cardiovascular effects (Babisch *et al*., 2005; Ising and Kruppa, 2004; Neus and Boikat, 2000). Moreover, there are likely other factors as well, because nationwide mortality statistics show

[2] Even though the Peters *et al.* (2004) investigators collected air pollution data for their traffic study, they did not explain in their NEJM article that there was no association between heart attack risk and PM or any air pollutant. A Letter to the Editor from the sponsoring agency (Health Effects Institute) (Tosteson and Greenbaum, 2005) stated that "air-pollution levels just before the myocardial infarctions [were] not associated with an increased risk of myocardial infarction."

correlations with calendar date (Phillips *et al*., 1999; 2001; 2004; Valberg, 2003). For example, Phillips *et al*. (2001) demonstrated that there is greater cardiac mortality among Chinese and Japanese Americans on days considered unlucky (*i.e.*, the fourth day of the month, given the Chinese and Japanese aversion to the number 4), consistent with the hypothesis that cardiac mortality is elevated by psychologically stressful occasions. If living in areas that have poorer air quality leads to stress, then such psychosocial factors are important for possibly confounding the long-term cohort associations between mortality and PM (Pickering, 2001; Moller *et al*., 2005; Everson-Rose and Lewis, 2005).

Another article relevant to whether increments in vehicle exhaust are causally related to increments in mortality is that of Kloner *et al*. (2009) "Comparison of total and cardiovascular death rates in the same city during a losing versus winning super bowl championship." The purpose of this study was to determine whether there were changes in community death rates when a local football team participated in a winning or losing Super Bowl. The Super Bowl-related days during LA's losing 1980 game were associated with higher daily death rates in LA County (per 100,000 population) for all deaths (2.4482 vs. 2.0968 for control days, $p < 0.0001$), circulatory deaths (1.3024 vs. 1.0665 for control days, $p < 0.0001$), deaths from ischemic heart disease (0.8551 vs. 0.7143 for control days, $p < 0.0001$), and deaths from acute myocardial infarctions (0.2710 vs. 0.2322 for control days, $p = 0.0213$). In contrast, the Super Bowl-related days during the winning 1984 game were associated with a lower rate of all-cause death (2.1870 vs. 2.3205 for control days, $p = 0.0302$). In conclusion, the emotional stress of loss and/or the intensity of a game played by a sports team in a highly publicized rivalry such as the Super Bowl can trigger total deaths and cardiovascular deaths. This study showed that air pollutants from LA "traffic congestion" during "winning" versus "losing" days had opposite effects on daily mortality. This goes contrary to an assumption of a causal link between increasing DEP and increasing mortality rates.

If PM-mortality/morbidity associations are confounded by factors that can vary with PM, but form no part of PM (or other combustion products more generally), then relying on the epidemiology associations to perform risk assessment for DEP makes no sense. The PM health-effect associations thus need to be carefully tested and re-evaluated to rule out alternative causal pathways. In the meantime, the inherent variability and uncertainty in these associations need be presented quantitatively (NRC, 2002).

In summary, the presence of numerous potential confounding variables that have not been ruled out makes the epidemiological associations difficult to interpret and reduces the weight that should be placed on these results *versus* other lines of evidence such as animal studies and controlled human exposure studies.

1.5 There is no reliable marker for partitioning the DEP part in generic ambient PM

Not only are the causal bases of the generic-ambient-PM *vs*. mortality / morbidity associations unknown, but also, such associations cannot be assumed to be applicable to DEP, which is only a small part of ambient PM. Ambient PM from monitoring sites is largely dominated by emissions from surface streets, and from gasoline vehicles; in addition, the apportionment of exhaust emissions between gasoline and diesel vehicles is highly variable by location (Fujita *et al*., 2007). Even more troublesome is the fact that no reliable marker exists specifically for the DEP component of ambient PM. Consequently, it is not feasible to undertake population epidemiology studies with regard to associations between "ambient DEP mass" and morbidity and/or mortality rates.

While some studies may use ambient elemental carbon (EC) and nitrogen dioxide (NO_2) as exposure surrogates for DE emissions, it is important to recognize that neither EC nor NO_2 in ambient air is a sufficiently specific marker for DE, due to the multitude of other common sources of these two pollutants. Thus, unacceptable uncertainties are associated with their use as markers of DE contributions to PM concentrations. In particular, Schauer *et al*. (2003) concluded that EC is not a unique tracer for DEP, pointing to EC emissions from gasoline-powered motor vehicles, coal-fired and fuel oil-fired power plants, incinerators, jet engines, wood-burning, and indoor sources (*e.g.*, church candles, cigarette smoke). NO_2 also has numerous common sources, including fossil fuel power plants, gasoline-powered vehicles, incinerators, as well as a number of indoor sources (tobacco burning, wood stoves, candles, and the use of gas-fired appliances and oil stoves), as well as many natural sources (intrusion of stratospheric nitrogen oxides, bacterial and volcanic action, forest fires, and lightning). If, for example, we had reliable measurement of personal NO_2 and/or EC exposure, there is no way to translate this into DEP exposure.

As the HEI report on "Diesel Exhaust" pointed out, diesel engine NO_2 emissions and DEP emissions often track in opposite directions, *i.e.*, for cooler-running engine conditions, NO_x emissions tend to be lower, but DEP emissions can be higher; for engines running at high temperatures, DEP emissions are reduced, but NO_x emissions may increase (HEI, 1995).

Study findings from researchers investigating day-of-week differences in the mean concentrations of a number of air pollutants (NO_x, O_3, VOCs, PM) raise further questions regarding the utility of NO_2 as an exposure surrogate for DE (Blanchard *et al*., 2008; Motallebi *et al*., 2003). In particular, while these studies have generally reported consistently lower NO_x concentrations for weekend days *versus* weekdays at numerous sites in different geographical areas (*e.g.*, Blanchard *et al*., 2008, who observed mean NO_x concentration declines of 49% for the time period 1998-2003 for monitoring sites in 23 states), more variable trends have been observed for PM and EC. For example, for the time period June 1998-August 1999, Motallebi *et al*. (2003) generally observed lower EC concentrations at five California monitoring

sites on weekends *versus* weekdays, but there was some variability in the size of these declines between locations. Importantly, these data suggested differing relationships between ambient NO_x and EC concentrations and well-established weekend-weekday changes in heavy-duty diesel vehicle traffic and miles traveled.

Finally, the ACES study demonstrated that, for new-technology diesel engines (NTDE), the EC component of DEP is small, as illustrated on the pie chart below (SwRI, 2009). Hence, EC would be a poor marker for DEP in ambient PM mass concentrations.

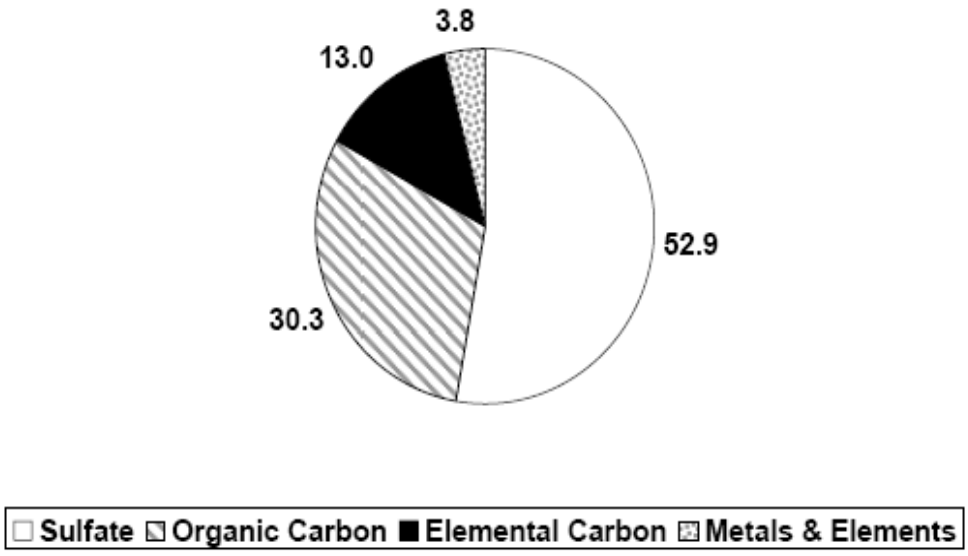


Figure 2.
As shown above, 2007 diesel technology engine PM is composed mainly of sulfate and organic carbon, with a small fraction of elemental carbon and metals and elements

2 Laboratory studies of animals and human volunteers inhaling DEP

Data from human volunteers inhaling controlled levels of diesel exhaust (DE) provide insights on the potential health effects of near-roadway DE exposures. These exposures to whole diesel exhaust have used DEP mass concentrations much higher than near-roadway exposures, yet the lung effects elicited include a mild, transient inflammatory response, and some evidence for transient thrombogenic and ischemic effects.[3] Moreover, chronic inhalation exposures with animal species at levels 10-30 times higher than near-roadway DE levels have reported an absence of adverse effects (see Figure 3 at the end of this text). Thus, experimental studies of DE exposure suggest a low potential for harm at the levels found near-roadways. Exhaust emissions from new-technology diesel engines, which are much lower than for older diesel technology, are expected to pose even less of a potential health concern.

2.1 Roadside levels of diesel exhaust represent upper-bounds of exposure

DE is a complex mixture that has components similar to gasoline engine exhaust, and a unique marker to measure near-roadway DE has not been established. Elemental carbon (EC) is frequently used as a measurement surrogate, because DE is the main source of EC along roadways. EC, however, is an imprecise measure of DE as there are other roadway and non-roadway sources that contribute to roadside EC (e.g., fossil fuel combustion, meat-cooking, biomass burning). On road measurements of DE or DEP can provide an upper bound for near-roadway DE levels, and DEP concentrations decline rapidly as one moves away, down wind from the roadway. In-vehicle exposure levels to DEP ranging from 6-33 $\mu g/m^3$ have been measured in California. EC exposures along a London street restricted to diesel trucks ranged from 4-16 $\mu g/m^3$. As new technology diesels replace aging diesels, and as diesels are retrofitted with the new emission control technology, these exposure levels can be expected to decline.

2.2 Reviews of DE health effects

Two integrative reviews of DEP non-cancer health effects are relevant to DEP risk assessment, namely, the USEPA 2002 Health Assessment Document for diesel exhaust, and the more recent, updated review of DEP health effects (Hesterberg *et al*., 2009). It is notable that the 2002 EPA review concluded that evidence for occupational exposure to DE causing non-cancer health effects was inadequate. Consequently, EPA, relying primarily on DE exposures to animals, derived a reference concentration (RfC) of 5 $\mu g/m^3$. That is, EPA judged the available chronic-exposure animal inhalation studies to be sufficient to

[3] Importantly, most of the DE data collected to date were for exposures to exhaust from older diesel engines, manufactured before emission regulations were mandated. With increasingly stringent emission standards, new technology diesel engines have been developed that provide dramatic reductions in diesel-engine emissions..

derive a lifetime-exposure reference concentration (RfC) of 5 μg/m^3 of diesel exhaust particulate (DEP). [4] This RfC is derived so as to represent an exposure level to which humans may be continuously exposed throughout their lifetime without being at appreciable risk of adverse noncancer health effects. The more recent review (Hesterberg *et al*., 2009), included consideration not only of animal exposures to DE, but also recent studies of human volunteers exposed to DE. Controlled human exposure studies at elevated exposure levels (*i.e.*, for DEP in the range 100 to 300 μg/m^3) largely support the pro-inflammatory role of DE for such exposures, but did not provide consistent support for the hypothesis that asthmatic and COPD populations are at greater risks of DE-induced respiratory effects. Controlled human exposure studies have provided results suggestive of cardiovascular health effects from short-term inhalation of DE at elevated concentrations. New laboratory animal studies continue to support the adjuvant effects of DEP on allergenic responses, as well as other immunologic effects including modulation of susceptibility to infection, with observed responses depending not only on dose and DEP source, but also on the timing of exposure and the animal species. However, the overall conclusion of the recent review was that, in the case of potential non-cancer health effects of DE, recent data support EPA's current human RfC, set at 5 μg/m^3, as being adequately health protective.

An important caveat to currently available data is that wide-ranging quantitative and qualitative changes have occurred in the composition of DE emissions, including marked reductions in PM emissions and polycyclic aromatic hydrocarbon (PAH) concentrations. That is, New Technology Diesel Exhaust (NTDE, *i.e.*, post-2006 DE) has physical and chemical characteristics that more closely resemble those of compressed natural gas emissions or gasoline engine emissions, rather than Traditional Diesel Exhaust (TDE, *i.e.*, unregulated pre-1988 DE). Very few animal studies and none of the human studies used DE from new technology diesel engines (NTDE), and additional data on health effects of NTDE emissions are necessary for risk assessment, because the diesel fleet is rapidly changing over to this new technology.

The NTDE *versus* non-NTDE difference is illustrated by McDonald *et al*. (2004), who investigated the relative toxicity of acute inhalation exposures (6 hrs per day over 7 days) for a baseline uncontrolled, traditional diesel exhaust (TDE) emissions case (approximately 200 μg/m^3 DEP) *versus* an emissions reduction (ER) case (low sulfur fuel, catalyzed ceramic trap, near background levels for all emissions but NO_x). They studied a suite of sensitive measures of acute lung toxicity in mice, including lung inflammation, RSV resistance, and oxidative stress. For the baseline TDE case, McDonald *et al*. (2004) observed statistically significant DE-induced effects for each class of responses, while these effects were either nearly or completely eliminated for the ER case. Despite the need to confirm these findings for a broader range of ER technologies and operating conditions and for other classes of health endpoints (*e.g.*,

[4] This RfC was derived from a 70-year-duration Human Equivalent Concentration (HEC) of DEP corresponding to a "No Observable Adverse Effect Level" (NOAEL) of 144 μg/m^3. Application of an uncertainty factor of 30 brings this NOAEL down to an RfC of 5 μg/m^3.

cardiovascular effects, allergenic effects), McDonald *et al*. (2004) concluded that their findings suggest that ER technologies can effectively reduce potential health hazards of DE exposures. Given findings such as those of McDonald *et al*. (2004), comprehensive toxicological investigations are needed to determine whether study findings of TDE and transitional DE apply to NTDE, including diesel engines with retrofitted particle traps and alternative diesel fuels.

It should also be noted that Seagrave *et al*. (2002) and McDonald *et al*. (2007) reported findings indicating that gasoline engine emissions can exert similar or even greater biological responses than diesel engine emissions. For example, McDonald *et al*. (2007) reported that inhalation of gasoline engine emissions resulted in many of the same respiratory and cardiovascular changes that were observed after exposure to elevated levels of DE.

2.3 Controlled DE-exposure studies with human volunteers

Controlled DE exposure studies with human volunteers have been conducted at inhaled DEP concentrations ranging from 100 to 300 $\mu g/m^3$, which are many-fold higher than levels found near roadways. That is, DEP concentrations in the human clinical studies are substantially higher than even estimates of short-term in-vehicle DEP concentrations (*e.g.*, 7.3 to 23 $\mu g/m^3$ from Fruin *et al*., 2004) and of roadway elemental carbon measurements (*e.g.*, 3.9 to 16 $\mu g/m^3$ from McCreanor *et al*., 2007).

2.3.1 Lung inflammation and immune system changes

The results of controlled DE exposure studies suggest that DEP concentrations on the order of 100 $\mu g/m^3$ are well-tolerated by the lung due to its protective antioxidant capacity, which prevents the occurrence of lung injury and inflammation. Results of elevated DE inhalation levels by asthmatic volunteers were variable, but with little evidence for greater adverse respiratory effects, compared to normal volunteers. Although human studies exhibit considerable heterogeneity, perhaps attributable to the source of DEP, the conclusions of the human studies suggest that the tested levels of DEP can elicit a mild, transient inflammatory response that is not highly adverse for either healthy individuals or asthmatics.

Laboratory animal studies of controlled exposures to elevated DE concentrations have reported changes in inflammatory markers, such as immunoglobulin levels, cell infiltration into the lungs, cytokine concentrations, reactive oxygen species, and susceptibility to infection. However, the results show considerable variability and inconsistency in allergic responses to DEP across animal species, disease model, study protocol, and particularly, among different sources of DEP. For example, some studies have concentrated on observed adjuvant effects of nasally-instilled or lung-administered DEP, with results

depending critically on the source of the DEP. Also, DEP doses were generally 50 times or more higher than would be achievable for typical, near-roadway levels.

Several large-scale animal experiments of multiple species have investigated chronic effects of DE inhalation on the respiratory system. These data indicate that highly elevated DEP doses (concentration × duration) can lead to chronic lung inflammation, but that lower doses, still much above typical levels of roadside DEP, yield little in the way of adverse or irreversible effects.

2.3.2 Cardiovascular health effects

Findings from human volunteers exposed to DE suggest some thrombogenic and ischemic effects of inhaled DE, albeit at exposure levels 10-15 times higher than typical roadside levels. Studies in laboratory animals provide some insights on the potential mechanisms underlying observed cardiovascular health responses (*e.g.*, abnormal electrical activity, increase in vascular inflammatory factors, platelet activation). But, given the use of unrealistically elevated DE exposure levels, the mechanisms identified by these studies may not be relevant at lower, near-roadway DE exposure levels.

2.3.3 Other health endpoints

Some findings in animals are suggestive of potential reproductive responses, such as increased testosterone levels and decreased spermatogenesis for considerably elevated DE exposures occurring during gestation (fetal development), but there is no evidence of reproductive responses at DE levels near the ranges typical of either occupational or ambient environments.

2.3.4 Occupational studies

Studies of occupationally exposed workers in the transportation industry (trucking, busing, and railroad), where DE levels were higher than near-roadway DE levels, show small associations with lung cancer risk (risk ratios generally below 1.5). Typically, however, no increase in lung cancer rates with increasing duration of employment or DE exposure has been found. Thus, a dose response for DE is lacking, and no causal relationship between DE and lung cancer risk in humans has been adequately demonstrated. The studies are also limited by a lack of quantitative concurrent exposure data and inadequate or lack of controls for potential confounders, particularly tobacco smoking. Furthermore, prior to dieselization, similar elevations in lung cancer incidence have been reported for truck drivers. These findings suggest that unidentified occupational agent(s) or lifestyle factor(s) might be responsible for the small elevations in lung cancer reported in the transportation studies. In contrast, underground miners in dieselized mines experience the highest occupational exposures to DEP, but do not show elevations in lung

cancer. Also, coal miners, the worker population most likely to have experienced "lung overload" in times past, do not show elevations in lung cancer.

2.3.5 Laboratory studies and cancer

Laboratory studies using rats exposed to high levels of DE over their lifetimes must be interpreted with caution with respect to predicting the carcinogenic potential of DE in humans (Hesterberg *et al*., 2005, 2006). Life-span bioassays in rats, mice, and hamsters have demonstrated that chronic inhalation of high concentrations of DE (> 1,000 $\mu g/m^3$ DEP) can cause lung tumors in rats, but not in mice or hamsters. Moreover, even in rats, a threshold level may have been identified below which no elevations in excess lung tumors were observed. Subsequent research has shown that, in rats, similarly high chronic exposures to particulate matter generally considered of low toxicity (such as carbon black and titanium dioxide) also can cause increased lung tumors in exposed rats. This appears to be the result of an overloading of the lung clearance of particles, which, in rats, leads to a build up of particles in the lung, sustained inflammation and cell proliferation, and eventually lung fibrosis and tumors. This mechanism of action would not be expected to occur in humans exposed under occupational or ambient conditions. For example, the occupation with historically the greatest lifetime lung burdens of inhaled particulate is coal mining, and although these heavy particle retentions have been shown to produce various lung diseases in coal miners, lung cancer is not increased among coal miners.

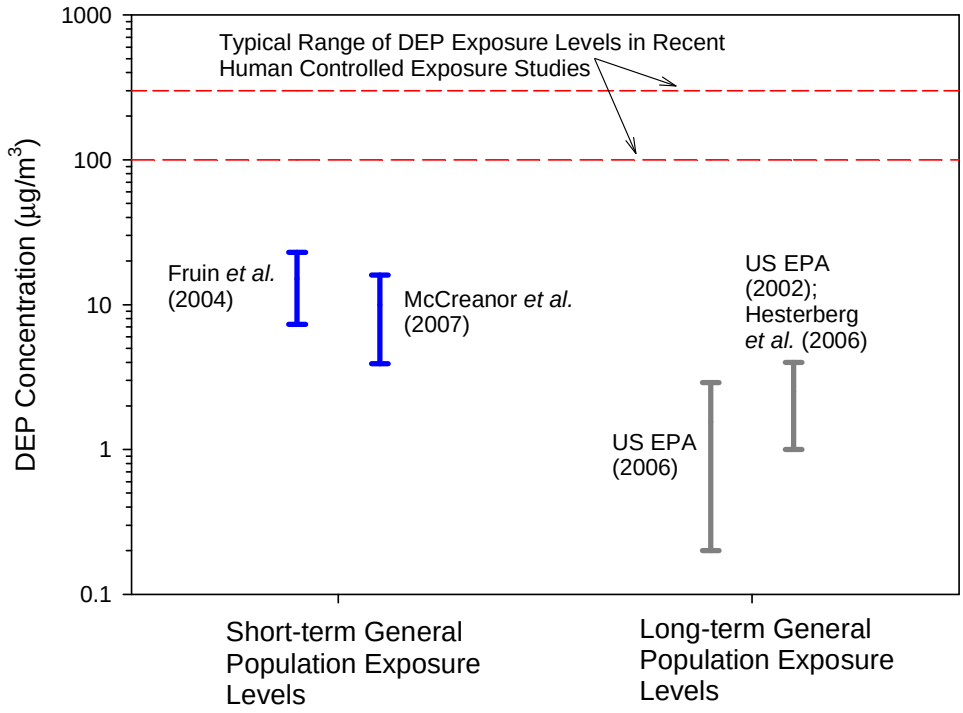
2.4 Conclusions from human volunteers and animals exposed to DE

Near-roadway levels of DE are typically much lower than those that have been used in controlled DE exposure studies with humans and laboratory animals. While high levels of DE may cause lung inflammation, cardiovascular, and immunological effects, the data suggest that current near-roadway DE levels do not pose a significant health concern. Emissions from new technology diesel engines, which are much lower than older diesel engines, are expected to result in near-roadway levels of DE that will be even less likely to be a cause of concern.

In addition to the use of elevated DEP concentrations, it is important to note that human volunteers in clinical studies of whole DE exposures are also typically exposed to highly elevated levels of gaseous DE constituents, including nitrogen dioxide, nitric oxide, and carbon monoxide. For example, Mills *et al*. (2005) measured an NO_2 concentration of 1.6 ppm for their human controlled exposure study of vascular dysfunction in healthy male volunteers, which is over 20 times higher than the median NO_2 concentration measured by McCreanor *et al*. (2007) along a heavily-trafficked London Street. As a result of the elevated exposures to gaseous DE constituents, there remains considerable uncertainty regarding whether the effects

observed in the human clinical studies of whole DE can be interpreted as attributable to DEP, or instead, attributable to DE gases.

Figure 3.
Range of Typical DEP Concentrations Employed in Recent Controlled Human Exposure Studies *versus* Ranges of Mean Short-term (*e.g.*, Hourly) and Long-term (*e.g.*, Annual Average) DEP Concentrations Representative of General Population Exposures



Notes:
1) Concentrations are on a logarithmic scale.
2) Source: Hesterberg et al., 2009.

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